An *in silico* method to identify computer-based protocols worthy of clinical study: An insulin infusion protocol use case

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ABSTRACT

Objective Develop an efficient non-clinical method for identifying promising computer-based protocols for clinical study. An *in silico* comparison can provide information that informs the decision to proceed to a clinical trial. The authors compared two existing computer-based insulin infusion protocols: eProtocol-insulin from Utah, USA, and Glucosafe from Denmark.

Materials and Methods The authors used eProtocol-insulin to manage intensive care unit (ICU) hyperglycemia with intravenous (IV) insulin from 2004 to 2010. Recommendations accepted by the bedside clinicians directly link the subsequent blood glucose values to eProtocol-insulin recommendations and provide a unique clinical database. The authors retrospectively compared *in silico* 18 984 eProtocol-insulin continuous IV insulin infusion rate recommendations from 408 ICU patients with those of Glucosafe, the candidate computer-based protocol. The subsequent blood glucose measurement value (low, on target, high) was used to identify if the insulin recommendation was too high, on target, or too low.

Results Glucosafe consistently provided more favorable continuous IV insulin infusion rate recommendations than eProtocol-insulin for on target (64% of comparisons), low (80% of comparisons), or high (70% of comparisons) blood glucose. Aggregated eProtocol-insulin and Glucosafe continuous IV insulin infusion rates were clinically similar though statistically significantly different (Wilcoxon signed rank test $P = .01$). In contrast, when stratified by low, on target, or high subsequent blood glucose measurement, insulin infusion rates from eProtocol-insulin and Glucosafe were statistically significantly different (Wilcoxon signed rank test, $P < .001$), and clinically different.

Discussion This *in silico* comparison appears to be an efficient nonclinical method for identifying promising computer-based protocols.

Conclusion Preclinical *in silico* comparison analytical framework allows rapid and inexpensive identification of computer-based protocol care strategies that justify expensive and burdensome clinical trials.

Keywords: computer/informatics, computer/health, comparison algorithms, preclinical/technical, preclinical investigations

INTRODUCTION

Decision-support tools can aid clinician decision-makers. Guideline and protocol use has produced favorable clinical outcomes.[1–4] Computer-based protocols can standardize clinical decisions while retaining the ability to adapt to contextual changes and thus individualize, or personalize, patient care.[5] In particular, computer-based protocols can enable replicable clinician decision-making (with clinician compliance of 95%) across cultures and medical specialties.[6,7] Computer-based protocols can also enable translation of research results to clinical practice.[8]

The advent of information technology in medicine has produced more computer-based protocols in different health institutions.[9–14] Clinicians may want to choose the best among alternative computer-based clinical protocols for use in clinical care or in a clinical trial. However, clinical trial evaluation of different computer-based protocols is challenging because of: 1) complexity of the clinical environment, 2) expense, 3) consumptions of time as well as clinical research and care resources, and 4) regulatory barriers.[15] An efficient method for comparing and assessing the performance of different computer-based protocols, before committing to an expensive and resource consumptive clinical trial, would be valuable.

Computer simulations have been widely used in medicine.[16,17] Clinicians can examine various use scenarios, safety issues, and patient benefits in a computer simulation without exposing patients to risk.[18] Allart *et al.*[19] described a strategy to compare computer-based protocols, but did not address specific methods. We know of no systematic computerized (*in silico*) comparisons of two computer-based protocols using real patient data unambiguously linked to the output of one of the protocols. A successful method could, quickly and inexpensively, identify alternative strategies worthy of clinical trial investment. To achieve this goal, we developed an *in silico* method for comparing alternative computer-based protocol care strategies. We present the first results of such a comparison of two computer-based insulin infusion protocols. We implemented a computer-based protocol (eProtocol-insulin) for management of ICU stress hyperglycemia.[6–8] eProtocol-insulin is an open-loop, servo-control, heuristic, rule-based, empiric protocol that recommends continuous IV insulin infusion rate. Its recommendations are based on the difference between the most recent blood glucose and the blood glucose target, the rate of change of blood glucose, the current continuous IV insulin infusion rate, the last concentrated IV glucose dose (if any, for treatment of hypoglycemia), and time.[6,8] Bedside clinicians review each eProtocol-insulin recommendation before adjusting the continuous IV insulin infusion rate. If the clinician declines the recommendation, the clinician will set the continuous IV insulin infusion rate according to his/her judgment. This is an iterative time-based method (at about 2 h intervals) that produces sequential blood glucose measurements following continuous IV insulin infusion rate adjustments. Bedside clinicians accepted 95% of eProtocol-insulin recommendations.[6–8] eProtocol-insulin has thus enabled a consistent and replicable clinician decision-making method.

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The resulting data collected in our electronic medical record (EMR) is unusual because it results from the direct interaction between the output of one of the protocols (eProtocol-insulin) and blood glucose measurements of ICU patients with stress hyperglycemia. This EMR database provides a unique resource for comparison of eProtocol-insulin with other replicable methods for managing stress hyperglycemia. We used it to evaluate Glucosafe, a candidate alternative computer-based protocol.

Glucosafe is a decision support system for glycemic control based on a multi-organ physiologic model developed in Denmark that recommends a continuous IV insulin infusion rate and an IV insulin bolus.[20–22] Glucosafe calculates insulin sensitivity based on blood glucose measurements, previous continuous IV insulin infusion rate and IV insulin bolus, and total parenteral and enteral nutrition. Glucosafe includes rules for insulin saturation effects and for the glucose absorption rate as a function of carbohydrate content in the gastrointestinal tract, based on the rate and type of enteral feeding.[21] Small-scale prospective studies have been conducted successfully in Europe to examine safety and performance issues.[20,22] The *in silico* method offers the opportunity for clinicians to examine a candidate computer-based protocol and compare it with eProtocol-insulin, before investing in a clinical trial. For the purpose of the comparison reported herein, the Glucosafe program was modified to accept batched sequential data input. The output of Glucosafe consists of an insulin sensitivity estimate, a continuous IV insulin infusion rate and an IV insulin bolus. The IV insulin bolus is only recommended when blood glucose exceeds 180 mg/dL.

METHODS

Glucosafe requires more input data than does eProtocol-insulin. To maximize the validity of Glucosafe results in our *in silico* comparison, we required perfect and complete data sets. We therefore eliminated a large number of data sets with any imperfection, however trivial (see Figure 1).

In some clinical circumstances, Glucosafe suggests an insulin bolus in addition to new settings for the insulin infusion. For the comparisons described below, we converted the Glucosafe IV insulin bolus into its continuous IV insulin infusion rate equivalent ($Insulin_{bolus\_iv\_equivalent}$), and added it to the continuous IV insulin infusion rate ($Insulin_{Glucosafe\_IV}$) to produce a total continuous IV infusion rate ($Insulin_{Glucosafe\_final}$), according to:

$$Insulin_{bolus\_iv\_equivalent}(U/h) = \frac{Insulin_{bolus}(U)}{\left(\begin{array}{c}time\ difference\ between\ two\ sequential\\ blood\ glucose\ measurements\ (h)\end{array}\right)} \quad \text{(i)}$$

$$Insulin_{Glucosafe\_final} = Insulin_{Glucosafe\_IV} + Insulin_{bolus\_iv\_equivalent} \quad \text{(ii)}$$

We examined LDS Hospital and Intermountain Medical Center EMR data from 2004 to 2010. We identified ICU patients at least 14 years old, with stress hyperglycemia managed with eProtocol-insulin and an 80–110 mg/dL blood glucose target.[6] We only included patients supported with eProtocol-insulin in single clinical encounters that contained >5 complete records of blood glucose and associated data (acquired at about 2-h intervals). We noted that while the target data acquisition interval was 2 h, the realities of delivering care in a clinical setting caused some variability (median = 2.05, standard deviation = 0.81, mean = 2.10 h). We extracted patient demographic records, blood glucose measurements, continuous IV insulin infusion rate, nutrition, IV propofol infusion rates (because of propofol's caloric value, used by Glucosafe), and presence and types of diabetes mellitus. Glucosafe uses quantified nutrition for computation of IV insulin recommendation, whereas eProtocol-insulin does not. We therefore excluded many patients because they were neither given enteral nor total parenteral nutrition. We excluded patients with recorded propofol infusion rates exceeding 200 mcg/kg/min. We excluded patients with two sequential measurements of blood glucose more than 12 h apart, to assure uninterrupted management of blood glucose with eProtocol-insulin.

eProtocol-insulin used blood glucose and insulin values at times t_i and t_{i-1}, to generate new continuous IV insulin infusion rate recommendations at time t_i (Figure 2). Glucosafe used blood glucose and insulin values at time t_i and at all previous times. For outcome evaluations, we used a moving window of two sequential times, t_i and t_{i+1}. The blood glucose at time = t_{i+1} was the outcome of the new continuous IV insulin infusion rate recommended and given at time = t_i (see Analysis of Glucose at time = t_{i+1} in Figure 2). We used the subsequent blood glucose measurement value (low, on target, high) at time = t_{i+1} to identify if the continuous IV insulin infusion rate recommendation at time = t_i was too high, appropriate, or too low. The 80–110 mg/dL blood glucose target range was the target in the original eProtocol-insulin clinical application that provided the clinical data for our computer-based protocol comparison. We defined low and high blood glucose ranges as <80 mg/dL and >110 mg/dL, respectively, to simplify the analysis. We used the following evaluation strategy to identify which of the two continuous IV insulin infusion rate recommendations (from eProtocol-insulin or Glucosafe) was more favorable, because it was more likely to bring the blood glucose at time = t_{i+1} to the blood glucose target range of 80–110 mg/dL:

> If the blood glucose measurement at time = t_{i+1} was low (<80 mg/dL), the continuous IV insulin infusion rate was higher than desired and the lower of the two recommended continuous IV insulin infusion rates at time = t_i was "more favorable," because it would likely have the lower danger of hypoglycemia.
> If the blood glucose measurement at time = t_{i+1} was high (>110 mg/dL), the continuous IV insulin infusion rate was lower than desired and the higher of the two recommended continuous IV insulin infusion rates at time=t_i was "more favorable."
> When blood glucose at time = t_{i+1} was within target (80–110 mg/dL), the lower of the two recommended continuous IV insulin infusion rates at time = t_i was "more favorable" because it would likely have the lower danger of hypoglycemia. We used two methods to determine if the two recommended continuous IV insulin infusion rates were "equivalent" if they were equal (analysis "a") or if the higher infusion rate was within 10% of the lower infusion rate (analysis "b") (Figure 2, "a" and "b").

We analyzed two groups of data:

1. Recommended continuous IV insulin infusion rate at time = t_i (a continuous variable), and
2. Favorability of continuous IV insulin infusion rate at time = t_{i+1} (a categorical variable).

We used the Wilcoxon signed rank test to compare the distributions of recommended continuous IV insulin infusion rates at time = t_i (a continuous variable). We conducted one-sample z-tests for proportions to assess the proportion of eProtocol-insulin and Glucosafe pairs of recommended IV continuous insulin infusion rates that were not equivalent at time = t_{i+1}. We assessed if the more favorable fractions for eProtocol-insulin or for Glucosafe (categorical variables) at

time = t_{i+1} were significantly different from 0.5 expected from chance alone. We evaluated more favorable fractions for three categories of blood glucose measurement at time = t_{i+1}: low (<80), on target (80–110 with equivalence analyses [a] and [b]), and high (>110 mg/dL).

RESULTS

We took advantage of a clinical database generated during use of a computer-based protocol to manage hyperglycemia with continuous IV insulin infusions (eProtocol-insulin). We only used data associated with eProtocol-insulin continuous IV insulin infusion rate recommendations accepted by the bedside clinicians. We examined 118 377 eProtocol-insulin recommendations from 2560 patients. We excluded 2152 patients using the criteria listed in Figure 1, leaving 408 patients with 20 770 eProtocol-insulin recommendations. We removed the 3.7% of 20 770 eProtocol-insulin recommendations rejected by bedside clinicians and used only eProtocol-insulin recommendations accepted by bedside clinicians. We also removed another 1021 records because blood glucose at time = t_{i+1} was not available or because the records followed an eProtocol-insulin recommendation rejected by the bedside clinician. We analyzed a study sample of 18 984 eProtocol-insulin recommendations for 408 patients (11 with type 1, and 113 with type 2 diabetes; 241 males and 167 females) (Figure 1 and Table 1). The study sample unambiguously reflected the direct link between continuous IV insulin infusion rates recommended by eProtocol-insulin and the subsequent blood glucose measurement (a rare feature of EMR data).

The aggregated eProtocol-insulin and Glucosafe recommended continuous IV insulin infusion rates were clinically similar though statistically significantly different (Wilcoxon signed rank test $P = .01$): mean (3.9 U/h and 4.0 U/h), median (3.3 U/h and 3.5 U/h), standard deviation (2.7 U/h and 3.1 U/h), minimum (0 U/h and 0 U/h) and maximum (21.5 U/h and 21.8 U/h), respectively. In contrast, when we stratified the time = t_i continuous IV insulin infusion rates by the three blood glucose measurement categories at time = t_{i+1} (<80, 80–110, and >110 mg/dL), the recommended time = t_i IV continuous insulin infusion rates from eProtocol-insulin and from Glucosafe were not only statistically significantly different (Wilcoxon signed rank test, $P < 0.001$), but also appeared clinically different. Glucosafe IV insulin recommendations were more favorable than those of eProtocol-insulin in all three time = t_{i+1} blood glucose categories (Table 2).

For blood glucose <80 mg/dL, Glucosafe recommended lower median rates of IV continuous insulin infusion (1.5 U/h) than eProtocol-insulin (3.4 U/h) and Glucosafe's recommendations were more favorable 80% of the time (Tables 2 and 3). For blood glucose >110 mg/dL, Glucosafe recommended higher median rates of IV continuous insulin infusion (5.4 U/h) than eProtocol-insulin (3.3 U/h) and Glucosafe recommendations were more favorable 70% of the time (Tables 2 and 3).

Figure 1: CONSORT diagram of considered patients. We used strict exclusion criteria to maintain an unambiguous relationship between eProtocol-insulin recommended continuous IV insulin infusion and subsequent blood glucose measurements.

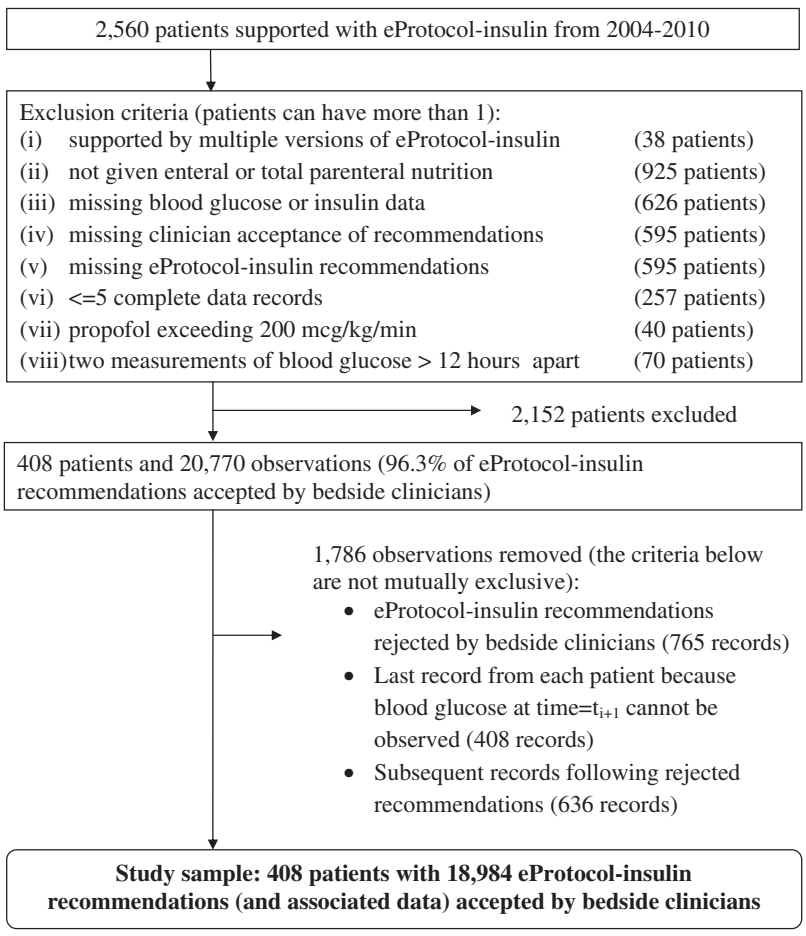
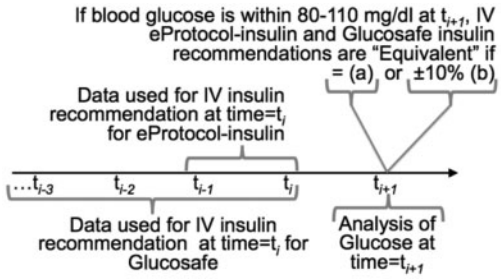


Figure 2: Temporal characteristics of eProtocol-insulin and Glucosafe. Times of data used for continuous IV insulin infusion rate recommendation and time of blood glucose used for assessment of the appropriateness of the continuous IV insulin infusion rate recommendation.



For blood glucose within the target range (80–110 mg/dL), Glucosafe recommended lower median rates of IV continuous insulin infusion (2.8 U/h) than eProtocol-insulin (3.3 U/h) and Glucosafe recommendations were more favorable 64% of the time for analysis (a) and 60% of the time for analysis (b) (Tables 2 and 3). Further, the proportion of IV insulin recommendations deemed more favorable (Table 2) was significantly different from 0.5 for both Glucosafe and eProtocol-insulin in each of the three blood glucose categories (one-sample *z*-test, $P < .001$).

DISCUSSION

We took advantage of a robust clinical database generated through use of a consistent clinician decision-making method (eProtocol-insulin) to perform an *in silico* comparison of two computer-based protocol care strategies (eProtocol-insulin and Glucosafe). Our use of eProtocol-insulin stabilized the clinical process of managing stress hyperglycemia in the ICU. This consistent, clinician decision-making method allowed us to use the clinical EMR data to rigorously evaluate Glucosafe and assess its worthiness for expensive and resource consumptive evaluation in a clinical trial. We were not evaluating the impact of either eProtocol-insulin or Glucosafe on pertinent clinical outcomes. We were not assessing the appropriateness of the protocol target of 80–110 mg/dL. Our analyses do demonstrate one effective way of evaluating a candidate computer-based clinical protocol and thus avoiding the unnecessary expense of conducting some clinical trials.

In aggregate, eProtocol-insulin and Glucosafe continuous IV insulin infusion rate recommendations at time $= t_i$ were statistically significantly different, but the difference appeared not clinically important. However when subdivided by blood glucose category at time $= t_{i+1}$, the continuous IV insulin infusion rate recommendations at time $= t_i$ were both statistically significantly different and the difference appeared clinically important (Tables 2 and 3). Glucosafe produced substantially more favorable insulin recommendations than eProtocol-insulin. In the low range, we expect Glucosafe's lower continuous IV insulin infusion rate recommendations would reduce hypoglycemia rates. In the high range, we expect Glucosafe's higher continuous IV insulin infusion rate recommendations would lower the blood glucose level to the desired range faster than does eProtocol-insulin. These results suggest Glucosafe is the preferable protocol and justify a formal clinical trial of Glucosafe.

Table 1: Demographic data and diagnostic groups

		Min	*Max*	*Mean (SD)*
Age (years)		14	95	49.5 (20.3)
Weight (kg)		39.5	275.8	86.3 (26.0)
Height (cm)		139.7	208.3	173.1 (10.3)
Primary Discharge Diagnostic Categories[a] (N patients)	Sepsis/Infection	90		
	Trauma	126		
	Pneumonitis	9		
	Respiratory, other	23		
	Cardiovascular	41		
	Abdominal	18		
	Liver	24		
	Gall Bladder/Pancreas	5		
	Malignancy	20		
	Diabetes Mellitus	2		
	Other Endocrine	1		
	Renal	7		
	Central Nervous System	2		
	Drug Overdose	21		
	Peripartum	4		
	Vasculitis	2		
	Other	8		

[a]408 patients total (241 male, 167 female). Diagnostic groups only available for 403 patients.

Glucosafe contains a comprehensive, multi-organ model, physiologic algorithm that incorporates detailed enteral and parenteral nutritional information.[21] eProtocol-insulin is an empiric rule set and has only a crude nutrition rule in its blood glucose management logic.[6] The Glucosafe protocol logic incorporates a more complete collection of relevant nutrition information than does eProtocol-insulin. This may explain why Glucosafe was able to more consistently recommend more favorable continuous IV insulin infusion rate than eProtocol-insulin. In spite of the ability of Glucosafe to function with more complex data, it actually proved superior even with the restricted clinical data available from previous eProtocol-insulin use. We might expect even better performance if more complex clinical data were made available to Glucosafe.

The clinical database, derived from patients supported with eProtocol-insulin, carries an imprint of the eProtocol-insulin logic. We expected this imprint of eProtocol-insulin logic to produce results that favor eProtocol-insulin; however, we observed the opposite. We believe this makes more credible the conclusion that the Glucosafe protocol logic produces more favorable IV continuous insulin infusion recommendations.

Our study sample was limited to Utah adult patients, predominantly Caucasians of northern European descent, who had been managed with eProtocol-insulin. A future comparison of eProtocol-insulin and Glucosafe, using clinical data generated with Glucosafe management and carrying the imprint of the Glucosafe logic, might be revealing. While we only compared two ICU insulin infusion protocols, the

Table 2: Favorability frequency

Recommended continuous IV insulin infusion rate at time $= t_i$[a]	Blood Glucose category (mg/dL) at time $= t_{i+1}$[a]	Favorability frequency, *n* (%)		
		eProtocol-insulin	Glucosafe	Equivalent
	<80	273 (15)	1470 (80)	102 (5)
a (continuous IV insulin infusion rate recommendations =)[a]	80–110	2919 (31)	5984 (64)	453 (5)
b (continuous IV insulin infusion rate recommendations ± 10%)[a]	80–110	2483 (26)	5573 (60)	1300 (14)
	>110	2045 (26)	5473 (70)	265 (4)

Counts of more favorable continuous IV insulin infusion rate recommendations at time $= t_i$ from eProtocol-insulin or Glucosafe, based on three blood glucose categories at time $= t_{i+1}$.

[a]Analysis (a) in Figure 1 (continuous IV insulin infusion rate recommendations of eProtocol-insulin and Glucosafe are equivalent only when they are equal). Analysis (b) in Figure 1 (continuous IV insulin infusion rate recommendations of eProtocol-insulin and Glucosafe are equivalent when they are within 10% of the lower continuous IV insulin infusion rate recommendation (±10%, b in Figure 2).

Table 3: Continuous IV insulin infusion rate recommendations and difference in recommended IV insulin infusion rate

Blood glucose category at time $= t_{i+1}$[a]	Count	Continuous IV insulin infusion rate recommendation (U/h) at time $= t_i$[a]		Pairwise continuous IV insulin infusion rate recommendation difference (U/h) at time $= t_i$[a]
		eProtocol-insulin median (IQR)	Glucosafe median (IQR)	(Glucosafe - eProtocol-insulin) mean (SD)
Low (<80 mg/dL)	1845	3.4 (3.5)	1.5 (3.2)	−1.8 (2.4)
On target (80–110 mg/dL)	9356	3.3 (3.2)	2.8 (3.6)	−0.8 (2.2)
High (>110 mg/dL)	7783	3.3 (2.8)	5.4 (4.7)	1.7 (2.9)
Total	18 984	3.3 (3.1)	3.5 (4.6)	0.1 (2.8)

Glucosafe minus eProtocol-insulin (U/h) at time $= t_i$, based on three blood glucose categories at time $= t_{i+1}$. We report medians (interquartile range) because the continuous IV insulin infusion rate recommendation distributions are skewed. We report the mean (SD) of the pairwise differences because the differences appear normally distributed.

[a]See Figure 2.

method we developed seems generally applicable to computer-based protocols, regardless of subject, as long as a clinical database is unambiguously linked to the performance of one of the computer-based protocols. One of the goals of future work is to explore more nuanced favorability scoring algorithms. We believe there is room to improve the algorithm by incorporating blood glucose trends and other clinically useful observations. We are preparing to launch a clinical trial that will compare eProtocol-insulin and Glucosafe based on the results of our *in silico* analysis reported herein.

Replicability of results is a general scientific requirement before new observations are embraced in a scientific domain. Replication of results generally requires replicable experimental methods. For clinical experiments this means a consistent clinician decision-making method. We believe this general scientific principle needs to be more widely embraced in medical research at the patient-clinician interaction.[5] Consistent clinician decision-making methods, enabled by computer-based protocols, will eliminate some unnecessary variation in clinical research and practice.[23] A consistent clinician decision-making method will stabilize part of the process of care and likely improve results in both clinical research and practice, just as stabilization of process has been associated with improvements in industry.[24]

We believe our *in silico* method can contribute to a Learning Health Care System.[25] The *in silico* comparison technique is an inexpensive method of identifying a computer-based clinical protocol that justifies the expense of a clinical trial. We can evaluate multiple computer-based clinical protocols of interest without incurring the cost of a full scale clinical trial. This could help to lower the overall cost of health care. The *in silico* method can also facilitate learning among researchers and clinicians. Lessons learned can be used to develop new knowledge and further improve the computer-based clinical protocol. The *in silico* method is a safe platform for comparing various use scenarios without engendering risk to patients.

Our results focus attention on the place of computer-based decision support tools in clinical practice. Traditional approaches designed to improve care through education alone are not likely to lead to achievement of healthcare delivery quality goals.[26] We believe electronic decision-support tools will be required.[27–30] Our strategy provides a proof of concept for an approach likely to be important in the future when more replicable clinical care methods are available. The current healthcare emphasis on EMRs, meaningful use, a Learning Health Care System, and reduction of error in clinical care make it

likely that more computer-based protocols like those described above will be forthcoming.

CONCLUSION

We performed a credible *in silico* comparison of two computer-based insulin infusion protocols. This *in silico* approach can be used to identify computer-based protocols worthy of the expense and burden of a clinical trial. Glucosafe appears worthy of clinical trial evaluation. Our analytical framework is one strategy for achieving some goals of a Learning Health Care System.

CONFLICT OF INTEREST

None.

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REFERENCES

1. Wirtschafter DD, Scalise M, Henke C, Gams RA. Do information systems improve the quality of clinical research? Results of a randomized trial in a cooperative multi-institutional cancer group. *Comput Biomed Res.* 1981;14:78–90.
2. Dawes R, Faust D, Meehl P. Clinical versus actuarial judgement. *Science.* 1989;243:1668–1674.
3. Johnston M, Langton K, Haynes B, Mathieu A. Effects of computer-based clinical decision support systems on clinician performance and patient outcome. *Ann Intern Med.* 1994;120:135–142.
4. Fox J, Patkar V, Thomson R. Decision support for health care: the PROforma evidence base. *Inform Prim Care.* 2006;14(1):49–54.
5. Morris A. The importance of protocol-directed patient management for research on lung-protective ventilation. In: Dreyfuss D, Saumon G, Hubamyr R, eds. *Ventilator-induced Lung Injury. Lung Biology in Health and Disease.* New York: Taylor & Francis Group; 2006: 537–610.
6. Morris AH, Orme J Jr, Truwit JD, *et al.* A replicable method for blood glucose control in critically Ill patients. *Crit Care Med.* 2008;36(6):1787–1795.
7. Thompson B, Orme J, Zheng H, *et al.* Multicenter validation of a computer-based clinical decision support tool for glucose control in adult and pediatric intensive care units. *J Diabetes Sci Technol.* 2008;2(3):357–368.
8. Morris AH, Orme J, Rocha BH, *et al.* An electronic protocol for translation of research results to clinical practice: a preliminary report. *J Diabetes Sci Technol.* 2008;2(5):802–808.
9. Hunt D, Haynes R, Hanna S, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. *JAMA.* 1998;280(15):1339–1346.
10. Vogelzang M, Zijlstra F, Nijsten MW. Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit. *BMC Med Inform Decis Mak.* 2005;5:38.
11. Shulman R, Finney SJ, O'Sullivan C, Glynne PA, Greene R. Tight glycaemic control: a prospective observational study of a computerised decision-supported intensive insulin therapy protocol. *Crit Care.* 2007;11(4):R75.
12. Bright TJ, Wong A, Dhurjati R, *et al.* Effect of clinical decision-support systems: a systematic review. *Ann Intern Med.* 2012;157(1):29–43.
13. Juneja R, Roudebush CP, Nasraway SA, *et al.* Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time. *Crit Care.* 2009;13(5).
14. Krikorian A, Ismail-Beigi F, Moghissi ES. Comparisons of different insulin infusion protocols: a review of recent literature. *Curr Opin Clin Nutr Metab Care.* 2010;13(2):198–204.
15. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. *Hastings Center Report.* 2013; 43(s1):S16–S27.
16. Sander C. Genomic medicine and the future of health care. *Science.* 2000; 287(5460):1977–1978.
17. Fone D, Hollinghurst S, Temple M, *et al.* Systematic review of the use and value of computer simulation modeling in population health and health care delivery. *J Public Health.* 2003;25(4):325–335.
18. Lateef F. Simulation-based learning: just like the real thing. *J Emerg Trauma Shock.* 2010;3(4):348–352.
19. Allart L, Vilhelm C, Mehdaoui H, *et al.* An architecture for online comparison and validation of processing methods and computerized guidelines in intensive care units. *Comput Methods Programs Biomed.* 2009;93(1): 93–103.
20. Pielmeier U, Andreassen S, Juliussen B, Chase JG, Nielsen BS, Haure P. The Glucosafe system for tight glycemic control in critical care: a pilot evaluation study. *J Crit Care.* 2010;25(1):97–104.
21. Pielmeier U, Andreassen S, Nielsen BS, Chase JG, Haure P. A simulation model of insulin saturation and glucose balance for glycemic control in ICU patients. *Comput Methods Programs Biomed.* 2010;97(3):211–222.
22. Pielmeier U, Rousing M, Andreassen S, Nielsen B, Haure P. Decision support for optimized blood glucose control and nutrition in a neurotrauma intensive care unit: preliminary results of clinical advice and prediction accuracy of the Glucosafe system. *J Clin Monitor Comput.* 2012;26(4):319–328.
23. Wennberg JE. Unwarranted variations in healthcare delivery: implications for academic medical centres. *BMJ.* 2002;325(7370):961–964.
24. Deming W. *Out of the Crisis.* Cambridge, MA: Massachusetts Institute of Technology, Center for Advanced Engineering Study; 1986.
25. Committee on the Learning Health Care System in America. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America.* Washington, DC: Institue of Medicine of the National Academies; 2013.
26. Mansouri M, Lockyer J. A meta-analysis of continuing medical education effectiveness. *J Contin Educ Health Prof.* 2007;27(1):6–15.
27. Jones JB, Stewart WF, Darer JD, Sittig DF. Beyond the threshold: real-time use of evidence in practice. *BMC Med Inform Decis Mak.* 2013;13:47.
28. Perez-Ruiz F, Carmona L, Yebenes MJ, *et al.* An audit of the variability of diagnosis and management of gout in the rheumatology setting: the gout evaluation and management study. *J Clin Rheumatol.* 2011;17(7): 349–355.
29. McGinn TG, McCullagh L, Kannry J, *et al.* Efficacy of an evidence-based clinical decision support in primary care practices: a randomized clinical trial. *JAMA Int Med.* 2013;173(17):1584–1591.
30. Stone PW, Pogorzelska-Maziarz M, Herzig CTA, *et al.* State of infection prevention in US hospitals enrolled in the National Health and Safety Network. *Am J Infect Control.* 2014;42(2):94–99.

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